

Targeted fortification for improved growth in preterm babies



With Prof Dr Christoph Fusch



Targeted fortification for improved growth in preterm babies

The survival rate for children born premature has increased substantially during the last two decades. One of the reasons behind this are improvements in the nutritional care of these infants. In 2010, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) issued their nutritional recommendations, but differences in breast milk macronutrient content between and within mothers can make achieving these recommendations challenging.

With colleagues at McMaster University in Canada, Prof Dr Christoph Fusch recently published a single-center, double-blinded, randomized controlled trial in Clinical Nutrition on how an individualized nutritional strategy called target fortification can help improve outcomes for preterm babies. Miris interviewed Prof Dr Christoph Fusch to hear more.

Can you shortly explain the concept of target fortification for our readers?

Some moms produce breast milk that is rich in nutrients, other moms produce breast milk that is low in nutrients. This variation affects all three macronutrients (i.e. fat, carbohydrates, and protein), but the changes are not related to each other. So, the variations are not just caused by a higher or lower water content, it is more complex than that. Some mothers deliver milk with high protein content, but not enough fat and some mothers do it the other way around, so there is a wide variety in the composition of the breast milk available in the NICU. In real NICU life, the assumption of a standard composition of breast milk does not apply and if we then add a standard fortifier babies are at risk of getting an unbalanced diet. However, if we would manage to measure what breast milk

contains and then add fortifiers to match the content, we would truly know what we end up with. Our goal is to achieve an intake according to ESPGHAN recommendations. For example, our goal is to have 8.0 grams of carbs per 100 mL, but if the measurement tells us that after standard fortification we would reach only 6.8 or 7.2 then we will add the missing carbs, and we will do the same for fat and protein. With this approach we fairly reach the ESPGHAN target, so babies get what they are supposed to get and we see appropriate growth that usually runs in parallel to their intrauterine percentile with an offset of -0.7 SD, which we believe is the correct ex-utero trajectory.

How did you come to start your research into nutritional care of preterm babies and target fortification? What's the story behind it?

The true story behind it is that one day in the 80s I heard the great neonatologist and former chief from Berlin, Professor Michael Obladen, saying we need to feed babies breast milk, but maybe we need more components than just standard fortification because it looks like only focusing on protein is not enough. He just put this idea into my head and when I became chair and chief in Greifswald, Germany, I started working on it and we saw that by improving



"I think it is all about education, about bringing the science and evidence to the bedside. We were lucky that we had really open-minded staff who said, yeah let's try it. We also admitted that if it doesn't work after a year then we stop it, but it worked, and even much faster, and so we did continue"

nutrition we got better growth. When I moved to Canada, I had the opportunity to really work on this concept by introducing bedside measurement of breast milk content. You know what, it's like blood gas analysis, but instead of adjusting the ventilator settings you adjust the fortification and then you get better results.

So why is it important to know the macronutrient composition of breast milk, isn't breast milk already optimal for babies?

Mother nature has adjusted the breast milk content to fulfill the needs of term babies, but breast milk

has a huge variability between mothers and also within the same mother. The good thing is that term babies can self-regulate their feeds. If they still feel hungry, they stay longer at breast, if the breast milk is rich in fat they drink less. They sense what the actual milk is composed of - in the same way as we as adults regulate eating depending on satiety feeling. For example, if we eat a cheese fondue or we eat fondue bourguignonne, we eat with at different speed and also with different duration as the fat and protein content of cheese fondue effects a faster satiety feeling already after a few bites. That is not different in term babies.

However, preterm babies do not have this chance to self-regulate because they are usually gavage fed, especially the tiny ones. Therefore, they must deal with what our neonatal team is filling into their stomach. While the biological components of breast milk are of superior digestive quality and tolerability, native breast milk per se is not perfect for preterm babies: these infants need approximately three times as much protein as the average content in breast milk, because their growth rate is three to four times higher compared to term babies. Also for fat there's a huge variability. Some moms only have 1 g/100 mL of fat in her milk and we would like to have 4.5 at least, while some moms have up to 6-7 g/100 mL.

Energy is needed to build up lean mass from amino acids and if you have an imbalance with not enough fat, then babies can't grow. That's why breast milk, which by digestibility and immunological properties is ideal, can lead to a dietary intake that is uncontrolled and might not be enough for up to 30 - 50 percent of the preterm babies even with standard fortification.

What is the risk for preterm babies if nutritional needs are not met, could you explain the need for growth for preterm babies?

Term babies grow at a rate of about 5-9 g/kg/day. Preterm babies grow up to 20 g/kg/day, so they have higher growth rates by a factor of two to four. Growth is mainly determined by buildup of lean mass and lean mass mainly means protein mass. Protein you get via amino acids, by ingesting protein. Growth is more or less a direct linear function of protein intake, more protein gives you more growth, less protein gives you less growth, provided that you have enough energy onboard.

If you don't give enough energy, you instead initiate protein breakdown. In this situation, the amino acids are being oxidized and are used for gluconeogenesis: the carbon skeleton is stripped off and fed into pathways of glucose metabolism. The remaining ammonium groups need to be excreted in the form of water-soluble urea, which is an energy and water consuming process. So, the two consequences of inappropriate intake are on one hand that the babies

don't grow sufficiently and, as a consequence, you will experience postnatal growth retardation, which means they are below their expected percentile or they lose percentiles. On the other hand, you can do metabolic harm because the protein is not utilized the way it should be but is excreted by forming urea. This process costs energy and a lot of water, as urea is a strong osmolyte and is the unfavorable metabolic pathway for protein.

Before we were able to measure milk composition, we sometimes saw babies where we tried to increase protein intake because they were not growing. Some of them deteriorated and looked septic, but there was no sepsis and there was no infection, nothing. Instead we saw that the urea went up massively, for example from 40 to 110 mg/dL.

"I am confident to say that when you do this approach the right way then it will work. I would like everyone to see our growth curves right now, they are unbelievable"

When we reduced protein intake babies came back to normal again. So, you can really make a baby sick with an unbalanced diet, giving too much protein compared to what they can build in.

When you started to analyze breast milk in your NICU what did you find?

We found the, already well-known, variability in macronutrients between and within mothers. What we also found, which was more unexpected, was that the content of macronutrients is not correlated, that moms with low protein do not necessarily have low fat and low carbs levels. It is not a question of a kind of diluted or concentrated milk. This finding was different from what we initially thought and from what was in the literature.

These results were published in Acta Paediatrica in 2015. If you plot the three macronutrients in a 3D-diagram you see a cloud of points, which means the levels are not correlated. For me, this finding was an eye-opener towards the true reason why a significant number of preterm babies cannot grow well on standard fortification. The current practice to fortify breast milk with a standard fortifier, which means adding fixed amounts of macronutrients, leads to these babies being fed a diet with a random composition - something that you would never decide to apply in daily routine. For example, we do not do that in parenteral nutrition and not in enteral nutrition, that one day we give 3.5 grams of fat and the next day we give 2.7 grams of fat, or we choose to give one day 3.8 g of protein and the next few days only 3 g of protein, but that is what we do to these babies when feeding standard fortified breast milk. It is appropriate for half of the babies where the breast milk composition is within the assumed limits, but not sufficient for the others. That is what we found, and we said this calls for action, let's see that we get rid of it, and then as a consequence we implemented the program of target fortification.

How long have you been running target fortification in your NICU as standard of care?

Here in Nürnberg we started about 18 months ago and it works beautifully. Everybody is now used to it and it is part of the daily routine. We do the measurements twice a week, on Mondays and on Thursdays, and all babies below 34 weeks get target fortification on a routine basis and we really have beautiful growth curves.

How are you set up in your NICU, who does the analysis and who prepares the feeds?

Feeds are prepared by the staff in the milk kitchen. Previously bedside nurses prepared the milk for their babies themselves, but we changed it so there's a dedicated nurse team who prepares the milk. We have a group of nurses who perform this task, but every day it is one dedicated nurse who prepares the milk for all our babies. We have a study coordinator who runs the analysis and gives us the data, and the doctors calculate the fortification with a standard algorithm. The recipes are then given to the milk nurses and they prepare the milk according to the recipe. It is not complicated; it



takes maybe five to ten minutes extra if you take everything together. It is a little bit of extra work, but it is all worth it as at the end you see really nice growth curves for the babies and realize that we can discharge babies earlier because they are metabolically more stable and keep their body temperature better, which are prerequisites for successful discharge at home.

How has target fortification been taken onboard by the nurses and the rest of the staff?

Our unit went through a transition with this new approach. Growth in the past was not optimal and NICU care was very much about lab diagnostics, ventilation and circulation. We have now expanded our focus on sepsis prevention and on nutrition and growth into daily routine. To achieve this, we started with lectures and educational sessions about why growth is important and how you can achieve appropriate growth, and if you care for growth you should also care for nutrition to impact growth and improve growth patterns. Then we gave educational sessions on the process of target fortification in the NICU. We started with the doctors first so that they understood, especially the attending and fellows, and then we also talked to nurses. They first had their concerns about workload, but as we started integrating target fortification into our routine and they could see the results and how beautiful the babies grow, nobody questioned to continue with this strategy.

I think it is all about education, about bringing the science and evidence to the bedside. We were lucky that we had really open-minded staff who said, yeah let's try it. We also admitted that if it doesn't work after a year then we stop it, but it worked, and even much faster, and so we did continue.

I am confident to say that when you do this approach the right way then it will work. I would like everyone to see our growth curves right now, they are unbelievable. We analyze the breast milk, adapt the fortification accordingly, and babies grow. And we have no side effects, we have no increased rate of NEC, people talk about milk curds, we do not see that. Babies just get what they are supposed to get, we do not do super fortification, that is the

most important point, it's really only that target fortification makes sure that all preemies get what they should have gotten all along.

Why are you so concerned about growth, why does it matter if the babies are growing or not?

Historically for many years or decades NICUs were focused on making preterm babies survive. The main research was on ventilation and only a few units were looking at feeding or growth. Feeding was frequently considered dangerous because of the risk to develop NEC, fluids were dangerous because of PDA and BPD and so on, so neonatologists in the earlier days got used to preterm babies not growing well. Everybody was happy if their weights moved somewhere and somehow in the growth charts, but many kids didn't grow well at all. We have data of cohorts that started with 30% SGA kids and at discharge there were 60-70% SGA, so in terms of growth we as neonatologists did a "lousy" job, and we got used to it.

That is why many neonatal staff saw undernourished preterm babies and this was considered as being normal. Literature is full of papers presenting such growth patterns, which today we would consider as inappropriate growth. With the modern paradigm shift on better growth you focus on feeding these babies more and as a consequence they grow differently, I'd like to say a bit more normal. With this practice you will see how these babies now visibly accumulate some more fat mass, but to our understanding that is normal, and nowadays we are also able to measure body composition and percent fat mass. So far, we do not have too robust data on what the appropriate trajectory of a preterm baby looks like once it left its intrauterine apartment.

We have further investigated this problem and were able to publish data on postnatal trajectories in a large cohort of preterm infants with mostly undisturbed postnatal transition – as a role model how "healthy" preterm infants would adapt to extrauterine conditions. We now are quite confident in assuming that these babies, once they are getting out of the uterus, drop their weight by 0.7-0.8

z-scores, and then continue to grow to get back to and merge with their corresponding WHO percentile a few weeks after term. We think that this pattern does reflect appropriate growth. If one would aim to follow that trajectory from the early beginning then one would avoid starving a baby, which then all of a sudden at around 34-35 weeks, when most babies - regardless what kind of NICU care they receive - get stable and you start feeding them better, will become obese. With target fortification we do not make them starve, already from the beginning we let them grow on this postnatal trajectory. We accept 0.7 z-scores difference to the intrauterine one, because we think that this is physiological because of the one-time, irreversible contraction of extracellular fluid space which results in a 7-12% loss of body water, and then keep them growing in that trajectory. Interestingly with the ESPGHAN recommendations on enteral intake, if you achieve them, you get exactly that kind of growth. But you need to start from the beginning, already during the first days of life. If you manage to do that, I think you will have the optimum outcome. We have looked into data for the long-term outcomes of kids where we compared different growth trajectories and we saw that coming close to “our” proposed trajectory really improves outcomes, and that’s why we think growth matters.

I think a lot of what is still in the literature comes from older studies where babies experienced different periods of growth: first insufficient intake and growth and then too high growth because once babies stabilized after this cautious initial approach, babies tolerated nutrition and staff may unintentionally have overfed babies to catch up. But that is not what we are aiming for. If you have patterns of slow initial growth leading to postnatal growth restriction then it might be better – once you are able to feed them more - if they grow slower, if you improve them more slowly. It may be similar to 14 -15-year-old adolescents who became anorexic and - if you feed them too fast - they might experience a refeeding syndrome and may even die, so you need to do that kind of refeeding very slowly. The same would be true in preterm infants initially exposed to growth restriction. However, our approach is to avoid this initial anorexic phase and

at any given day provide the baby with appropriate nutrient intake so they can accumulate that body composition that they would have accumulated in utero. But to “play” this approach it is definitely helpful to know a little bit about nutrition and growth physiology, and why it is so important to ensure that we give a balanced diet - something which many neonatologists are not aware of and don’t do today.

You say that you see improvement in clinical outcomes, what clinical outcomes are you looking at?

On one hand we studied short-term outcomes which is just anthropometry, head circumference, length and weight. We have also done body composition at McMaster and we will do it very soon also in Nürnberg.

Then in a more sophisticated way you can also compare metabolic parameters and look at triglycerides, hormones, glucose etc, and also blood pressure, as well as other metabolic markers that are linked with early onset of adult diseases. You should also investigate neurodevelopmental outcome at the age of two or five years, or even later.

We have also looked into complications during the hospital stay and we found less sepsis and interestingly also lower NEC rate with target fortification. It was not statistically significant at a 5% level, but the trend was clear. We also found less feeding intolerance. We believe this is because the baby gets the same composition every day and not one day a lot of fat and then less fat and so on, and the gut is working under more steady state condition.

Is your feeling that your targets for nutrition are met in your NICU?

Yes totally. We have very few babies that do not grow despite sufficient intake. These babies apparently seem to not digest well and experience an additional problem, like relative exocrine pancreatic insufficiency, and is therefore not reaching the expected trajectory. That has been reported, but this is in maybe one out of 50 babies, and for these babies we investigate other digestive issues.

What would your advice be if you were talking to a NICU director that is doing standard fortification, but thinking about changing to target fortification? Where would you advise them to start?

First, I would propose that they come over to our unit to see how we are doing it, because it's running smoothly in routine here and that could be encouraging for them.

If I realize that they are experiencing compliance problems with their team, then I would ask:

- Question: Are you ventilating babies?
- Answer: Yes
- Question: On a ventilator?
- Answer: Yes
- Question: Are you doing blood gas analysis?
- Answer: Yes, why are you asking?
- Question: Why are you doing blood gas analysis?
- Answer: Because I have a baby on the ventilator and I need to guide the settings
- Question: Do you know any kind of randomized controlled blinded trials that compare ventilator respiratory management with and without using a blood gas machine?
- Answer: No
- Question: Then why are you using blood gas analysis in ventilated babies? There's no evidence that using a blood gas machine is useful, but you are using it.

Now go to nutrition, there is now some evidence that measuring breast milk content will improve growth. You are using a blood gas machine without

evidence, but you won't analyze breast milk though there is evidence. What is the rationale behind that behavior? And - with breast milk analysis you don't even need to take blood. You just take breast milk, you get it for free, it is a painless procedure and you measure nutrient contents precisely, at the same speed as you do using a blood gas machine and then you take the data, do a quick calculation, fortify accordingly, and then you see one or two days later that growth improves, why aren't you doing it already?

Once you understand that breast milk composition is not always the same, then you also understand that you're feeding the same baby a different diet every day. We would not accept that strategy in any other part of the care of these babies.

I think the ESPGHAN recommendations are very sound and they are based on a lot of nutritional physiology research from the 70s, 80s and 90s - research which nobody's doing anymore. The data is very consistent overall and from my experience, if you really manage to provide ESPGHAN recommended intakes to these babies then 95 percent of the babies will grow, whereas if you don't meet these intakes the babies won't grow.

With your recent findings do you see a future for target fortification as standard of care for preterm babies?

For us it now has become standard of care, but it might take another 5-10 years until other units are

"Once you understand that breast milk composition is not always the same, then you also understand that you're feeding the same baby a different diet every day. We would not accept that strategy in any other part of the care of these babies."

ready to adopt it as standard care. In this context it needs to be mentioned that currently some studies claim to do target fortification, but unfortunately reduce it to adjusting only protein intake, forgetting to also look at energy intake which is of equal importance. Such approaches violate nutritional physiology and they add a lot of nutritional research noise and it might take a while until that is all cleared out. But I for sure see target fortification as the standard of care for preterm babies in the future.

When Bo Lönnerdal and Staffan Polberger in the 90s in Sweden showed that by analyzing breast milk and subsequently fortifying according to content, you could improve growth of preterm babies, Swedish NICUs changed their practices in the following years. Why do you think the rest of the world didn't follow, what is the hang-up on actually implementing this practice?

That's a good question. Look at what happened with respiratory support: in the 80's everybody was on mechanical ventilation and later also to replace surfactant. However, Sweden already in the 70s and 80s provided non-invasive respiratory support using CPAP. Other parts of the world were not interested in doing so, they were just ignoring it. However, some 30 years later - thanks to the CPAP inventors, thanks to the Swedish guys, but also thanks to Jen-Tien Wung at Columbia Babies Hospital in New York, CPAP was in the end adopted world-wide. It finally had to do with intelligent adaptation of findings that influence clinical practice, and this is the same with nutrition. Sweden is a small country, so people say who cares what they do, right? But they were right, and I can only support that they were fully right to do so.

How come you chose the Miris HMA for your NICU in Nürnberg?

The Miris was validated by our group, and so we know that it works. We also like the device because it's small and easy to handle. And also support was good, Miris support has really improved over the last 10 years. I must say Miris has really taken on the challenge that in part was also opened by us by the results obtained in the validation studies. Miris has taken that on and continuously worked on improving their device, which I cannot say is true for other

bedside milk analysis devices. And I'm not paid by Miris, I want to say I'm independent.

You just published a study on target fortification in Clinical Nutrition, what did you find?

We found that babies that get target fortified breast milk grow better. One very interesting finding is what we found when we did subgroup analysis. If we look at the group of babies whose mothers produce breast milk with naturally high protein, the effect of the intervention is relatively small. And honestly, that was to be expected from existing physiology data. But for those whose mothers produce breast milk with naturally low protein content, the difference between the intervention and non-intervention group was massive with about 350 grams of weight difference. There was only a small increase in fat mass, which is normal, but they experienced mainly an increase in lean mass.

I think in all honesty it's the only trial that has been made with a validated device and by using good laboratory practice and by adjusting all the components, namely protein, fat and carbs individually, and therefore really met the ESPGHAN recommendations.

Are you measuring BUN in your unit or are you confident that you're not overshooting on proteins?

We are measuring BUN every other week, that was already part of the standard practice before I took over the unit, but we rarely need to adjust our feeding prescriptions. We seldom see high BUN, which might be due to the fact that we provide a balanced diet with this kind of approach.

How is the set-up in your NICU? Are parents able to stay in the NICU with their babies?

No, we unfortunately don't have enough space. We are planning a new Children's Hospital, but currently it's not possible. Moms stay at home or they can stay here in the hospital, but not in the NICU. We have an open-door policy; parents can visit whenever they want. We have two mother-child rooms, but those are for the families when our patients are coming close to discharge.



Are your parents still allowed on the unit in the current covid-19 situation?

We allow both parents to visit, there are no restrictions as long as both are healthy and don't show any covid-19 associated symptoms. We recently had kids from covid-19 positive parents in the unit, but that's a different story. It may become hard, but as long as relatives are covid-19 positive, they are not allowed in. But other than that, we allow both parents in the unit. This is important: if you get a new child it's not only the mother-child dyad that needs to be established, if there is a partner then it is equally important for the partner to be able to form that bond as well.

If a covid-19 positive mother gives birth to a preterm baby, do you consider the baby to be positive or negative?

We are in discussion on that topic right now. I think the risk of transition is relatively low so we would rather like to consider them as covid-19 negative, but of course we follow the directions given by our infection control though sometimes they have a different opinion. They consider them as positive and we need to test them and continue for 14 days at least and until then they should be in a single room. But we sometimes are running short on space, so I think we are still trying to find the tools there. It's hard times for everyone.

The full publication can be found here:

<https://www.sciencedirect.com/science/article/pii/S0261561420302028>

Individualized target fortification of breast milk with protein, carbohydrates, and fat for preterm infants: A double-blind randomized controlled trial.

Niels Rochow, Gerhard Fusch, Anaam Ali, Akshdeep Bhatia, Hon Yiu So, Renata Iskander, Lorraine Chessell, Salhab el Helou, Christoph Fusch
Clinical Nutrition May 2020, in press



www.mirissolutions.com